UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/811,793	03/29/2004	John R. Plachetka	7569/80993	2542

7590 04/06/2006

Michael A Sanzo
Fitch Even Tabin & Flannery
1801 K Street NW
Suite 401L
Washington, DC 20006-1201

EXAMINER	
CHOI, FRANK I	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 04/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/811,793	PLACHETKA ET AL.	
	Examiner	Art Unit	
	Frank I. Choi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-29 and 34-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-29 and 34-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

The amendment filed 12/29/2005 with respect to the Specification and claims does not comply with 37 CFR 1.173(b), which sets forth the manner of making amendments in reissue applications. Further, any amendments to the Specification and claims must be made vis-à-vis the original patent specification and claims and not in relation to a prior amendment. See 37 CFR 1.173(g). Deletions must be represented by brackets not strikethrough. See 37 CFR 1.173(d). The status identifiers under 37 CFR 1.121 are not applicable in a reissue application. Further, other than indicating the cancellation of a claim and the parenthetical use of "amended", "twice amended" etc. with respect to an original patent claim, the status of all claims, i.e. pending or canceled, along with an explanation of the support in the disclosure for changes made to the claims must be provided in a separate paper. See 37 CFR 1.173 (b) and (c). See MPEP Section 1453 [R-3] for proper reissue amendment practice.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-29, 34-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for acid-base storage stabilized dosage forms in which metoclopramide and/or analgesic are barrier coated or are in separate layers of a multilayered dosage form separated by intermediate layer containing no metoclopramide and analgesic and coordinated dosage forms in which the analgesic or matrix containing the same is barrier coated

or formulated to delay release and the metoclopramide is immediately releasable either from the same matrix or a separate layer does not reasonably provide enablement for undisclosed acid-base stabilized dosage form or undisclosed coordinated dosage forms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The nature of the invention:

The invention is directed to a pharmaceutical composition in unit dosage form comprising metoclopramide and analgesic in acid-base storage stabilized form and/or metoclopramide and analgesic in coordinated dosage form.

The state of the prior art and the predictability or lack thereof in the art:

The prior art of record does not appear to disclose other acid-base storage stabilized forms other than forming a barrier coating or addition of the active agents into separate layers of a multi-layered dosage form separated by another layer which does not contain the incompatible ingredients or the separate coordinated delivery of metaclopramide and analgesic in a single dosage form. See Pescetti (US Pat. 3,939,259), Column 3, lines 25-33; Buckwalter et al. (US Pat. 2,768,115), Columns 2-6.

The amount of direction or guidance present and the presence or absence of working examples:

The Specification only discloses the use of barrier coatings, separate layers separated by a layer which contains neither metoclopramide nor analgesic or separate layers in which the metoclopramide layer releases faster than the analgesic layer.

The breadth of the claims and the quantity of experimentation needed:

The claims are broad in that the terms "acid-base storage stabilized form" and "coordinated" define an intended effect but not how the intended effect is supposed to be arrived at other than through the use of barrier coatings and separate layers separated by layer which contains neither of the incompatible drugs. As such, it appears that one of ordinary skill in the art would be required to do undue administration to determine other acid-base storage stabilized forms other than the use of barrier coatings or separate layers separated by layer containing neither metoclopramide nor analgesic and how to sequentially deliver the active agents when the active agents are in a single dosage form other than the use of barrier coatings and/or separate layers which is formulated such that metclopramide is released faster than the analgesic.

Examiner, by not rejecting claim 8, implied that there was sufficient enablement to simply claim that the metoclopramide and acidic analgesic would in separate layers. However, upon further consideration, the use of separate layers still permits an embodiment in which metoclopramide and the acidic analgesic come in to contact, i.e. where the separate layers are adjacent to each other. Where acid-base storage stability is desired there appears to be only three options available: (1) barrier coating around at least one of the metoclopramide and incompatible analgesic; (2) separate layers which are adjacent and use of said barrier coating; and (3) separate layers which are separated by a layer which contains neither metoclopramide or incompatible analgesic. Where coordinated delivery is desired the only options available are the use of barrier coatings and/or separate layers with the proviso that whatever variation is used that the barrier coatings and/or separate layers are formulated such that metclopramide and the analgesic are released and achieve therapeutic levels at the defined time. As such, in both cases barrier coatings and/or separate layers appear to be the way to achieve stability and/or coordinated

delivery. The acid-based storage stability claims lack scope of enablement because the same include embodiments in which the separate layers can be contact and the coordinated dosage form claims lack enablement because the use of barrier coatings and/or separate layers which are formulated to achieve sequential administration as defined by the Specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5-29, 34-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hsiao et al. (U.S. Pat. 5,885,616) in view of Poyser et al. (U.S. Pat. 4,325,971), Tfelt-Hansen et al. (Lancet 1995; 346:923-926), Pradalier et al. (Headache 28: 550-557, 1988), Beubler, Mandell, Ferrari et al., Ross-Lee et al. (Eur J. Clin Pharmacol (1983) 24: 777-785) and Bru et al. (US Pat. 5,437,874).

Hsiao et al. teaches multilayered dosage forms where the outer layer is immediately released whereas the inner layer is sustained release which are separated from each other by a polymer layer in which aspirin and metoclopramide are taught as a suitable drugs (Columns 2, 3, Column 5, lines 15-49).

Poyser et al. teach the combination of an analgesics, such as coated paracetamol, paracetamol or acetylsalicylic acid and the like in single dosage forms for the treatment of migraine and that metoclopramide potentiates the effects of analgesics (See entire document).

Tfelt-Hansen et al.discloses that the most commonly used drug for treatment of migraine is aspirin but that during migraine attacks aspirin absorption is delayed due to gastric stasis (Pg. 923). It is disclosed that metoclopramide is combined with aspirin to return the absorption of aspirin to normal during migraine attacks, enhance the effect of aspirin and combat nausea and vomiting (Pg. 923). It is disclosed that sumatriptan is expensive and has adverse effects (Pg. 925).

Pradalier et al. discloses that NSAIDs, such as aspirin and naproxen, are effective in treating migraine (See entire document).

Beubler disclose that aspirin, acetaminophen, ibuprofen, naproxen and metoclopramide are used to treat migraine and that the side effects of ergotamine and dihydroergotamine are troublesome (Abstract).

Mandell teaches that selective cyclooxygenase-2 inhibitors, such as celecoxib, are as effective as other NSAIDs, but cause less GI ulceration and bleeding (Abstract).

Ferrari et al. disclose that use of serotoninergic vasoconstrictors such as sumatriptan and ergotamine although effective can result in recurrence of migraine or rebound headache (Abstract).

Ross-Lee et al. teach that pretreatment with metoclopramide overcomes the reduced gastro-intestinal motility associated with migraine and results in faster delivery of aspirin (See entire document).

Bru et al. discloses that mixtures of acetylsalicylic acid and metoclopramide are unstable (Column 1, lines 48-51).

The difference between the prior art and the claimed invention is that the prior art does not expressly disclose the combination of metoclopramide and naproxen in acid-base storage stabilized dosage form, the combination of metoclopramide and analgesic, drug or non-acidic analgesic in coordinated dosage forms, the combination of metoclopramide and analgesic in an acid-base storage stabilized dosage form in which said metoclopramide and said analgesic are each in separate layers of a multilayer tablet, or the combination of metoclopramide and analgesic where the dosage form is an acid-base storage stabilized and coordinated dosage form. However, the prior art amply suggests the same as multi-delivery and multi-layered dosage forms, the combination of metaclopramide and analgesics, such as NSAIDs, are disclosed in the prior art. Further, the prior art discloses pretreating with metaclopramide when administering analgesics, such as NSAIDs, for treatment of migraine. As such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to modify the prior art as above with the expectation that analgesics, such as NSAIDs, as a class would be effective in treating migraine and that metoclopramide would increase the effectiveness and absorption of the analgesic. Further, one of ordinary skill in the art would have been motivated to formulate a dosage form wherein metoclopramide is in the immediate release layer and the analgesic is in the sustained release layer as it is known that pretreatment with metoclopramide overcomes the reduced gut motility associated with migraine, with the expectation that sustained release of the analgesic would increase effective treatment time and require less dosing, that the separation of the metoclopramide and analgesic into different layers would prevent any adverse interaction and that a single dosage form would be more convenient to administrate than separate dosages of different drugs. Finally, although an acid-base storage stabilized form is not explicitly disclosed,

Hsaio discloses a polymer layer between the immediately releasing layer and the sustained release layer, as such, the metoclopramide contained in the immediately releasing layer and the analgesic in the sustained release layer will not interact during storage. Further, one of ordinary skill in the art would be motivated to separate the analgesic from the metclopramide, at least one analgesic/metoclopramide combination has be found to be unstable.

Examiner has duly considered Applicant's arguments but deems them unpersuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

With respect to the minimum time of 5 minutes for the analgesic to achieve therapeutic levels, the prior art suggests sequential administration at an interval of 3 minutes and formulation of a unit dosage form having immediate and slower release in the same unit dosage. As such, it would be well within the skill of one of ordinary skill in the art to formulate the unit dose to achieve sequential administration, i.e. coordinated, and vary the timing as necessary to achieve the desired increased effect of the analgesic. See In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C

and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.).

Applicant argues that Ross-Lee does not suggest that simultaneous administration of drugs would not have been equally effective or that another hypothetical motivation may suggest providing an immediate release and slow release of metoclopramide. However, this does not preclude the suggestion or motivation to separate metoclopramide and the analgesic as indicated. Contrary to Applicant's arguments, the combined teachings of the prior art suggest and provide motivation for pre-release of metoclopramide. Since it is disclosed that pre-administration of metoclopramide results in increased availability of the analgesic and that immediate and slow release can be achieved in a single dosage unit, it would be well within the skill of one of ordinary skill in the art to formulate a unit dosage form which immediately releases metoclopramide and slowly or delays release of the analgesic with the expectation that the unit dosage form would be easier for a patient to take than two separate pills and that the unit dosage form would achieve the same or similar result as sequential administration.

Contrary to Applicant's arguments, there is no evidence that the coordinated dosage form is so different from sequential administration that sequential administration would not suggest a coordinated dosage form or that sequential administration would not result in an overlap in drug release. Applicant's own definition permits a temporal lapse from any where from 4-59 minutes.

There is no requirement that pre-administration must be preferable to simultaneous administration, it is sufficient that the prior art provides the motivation to formulate a unit dosage

form which achieves the effects of sequential administration. Applicant acknowledges that migraines can last for long periods of time, as such, even if most migraines may be short in duration, this does not overcome the motivation to provide sustained release of the NSAID. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Claims 5-29, 34-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (US Pat. 4,938,967) in view of Raff (US Pat. 3, 279,998), Poyser et al. (U.S. Pat. 4,325,971), Tfelt-Hansen et al. (Lancet 1995; 346:923-926), Pradalier et al. (Headache 28: 550-557, 1988), Beubler, Mandell, Ferrari et al., Ross-Lee et al. (Eur J. Clin Pharmacol (1983) 24: 777-785) and Bru et al. (US Pat. 5,437,874).

Newton et al. teaches a tablet dosage form, which combines an immediate release component and a sustained release component in which metoclopramide is taught as a suitable drug (Column 7, 10-24, Column 8, lines 18-31, Column 13, line 2)

Raff et al. discloses a sustained release tablet containing an immediate release layer and a sustained release layer (Column 4, lines 21-38).

Poyser et al., Tfelt-Hansen et al., Pradalier et al., Beubler, Mandell, Ferrari et al., Ross-Lee et al. and Bru et al. are cited here for the same reasons as above and are incorporated herein to avoid repetition.

The difference between the prior art and the claimed invention is that the prior art does not expressly disclose the combination of metoclopramide and naproxen in acid-base storage stabilized dosage form, the combination of metoclopramide and analgesic, drug or non-acidic analgesic in coordinated dosage forms, the combination of metoclopramide and analgesic in an acid-base storage stabilized dosage form in which said metoclopramide and said analgesic are each in separate layers of a multilayer tablet, or the combination of metoclopramide and analgesic where the dosage form is an acid-base storage stabilized and coordinated dosage form. However, the prior art amply suggests the same as multi-delivery and multi-layered dosage forms, the combination of metaclopramide and analgesics, such as NSAIDs, are disclosed in the prior art. Further, the prior art discloses pretreating with metaclopramide when administering analgesics, such as NSAIDs, for treatment of migraine. As such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to modify the prior art as above with the expectation that analgesics, such as NSAIDs, as a class would be effective in treating migraine and that metoclopramide would increase the effectiveness and absorption of the analgesic. Further, one of ordinary skill in the art would have been motivated to formulate a dosage form wherein metoclopramide is in the immediate release layer and the analgesic is in the sustained release layer as it is known that pretreatment with metoclopramide overcomes the reduced gut motility associated with migraine, with the expectation that sustained release of the analgesic would increase effective treatment time and require less dosing, that the separation of the metoclopramide and analgesic into different layers would prevent any adverse interaction and that a single dosage form would be more convenient to administrate than separate dosages of different drugs. Finally, although an acid-base storage stabilized form is not explicitly disclosed,

Poyser et al. discloses coated paracetamol, as such, the paracetamol in the coated paracetamol willl not interact with the metoclopramide during storage. Further, one of ordinary skill in the art would be motivated to separate the analgesic from the metclopramide, at least one analgesic/metoclopramide combination has be found to be unstable.

Examiner has duly considered Applicant's arguments but deems them unpersuasive for the same reasons as above.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Claims 5-7, 9-29, 34-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shah et al. (US Pat. 6,126,969) in view of Poyser et al. (U.S. Pat. 4,325,971), Tfelt-Hansen et al. (Lancet 1995; 346:923-926), Pradalier et al. (Headache 28: 550-557, 1988), Beubler, Mandell, Ferrari et al., Ross-Lee et al. (Eur J. Clin Pharmacol (1983) 24: 777-785) and Bru et al. (US Pat. 5,437,874).

Shah et al. discloses a tablet or capsule containing an active pharmaceutical principle which is coated to provide controlled sustained release of the active ingredient which is combined with an uncoated pharmaceutically active ingredient which can be different from the sustained-release coated pharmaceutically active ingredient and that the active ingredients can include migraine treatments, metoclopramide and anti-inflammatory drugs such as indomethacin, naproxen, ibuprofen or flurbiprofen (Column 5, lines 45-60, Column 6, lines 1, 11, 13,14, Column 7, lines 7-15).

Poyser et al., Tfelt-Hansen et al., Pradalier et al., Beubler, Mandell, Ferrari et al., Ross-Lee et al. and Bru et al. are cited here for the same reasons as above and are incorporated herein to avoid repetition.

The difference between the prior art and the claimed invention is that the prior art does not expressly disclose the combination of metoclopramide and naproxen in acid-base storage stabilized dosage form, the combination of metoclopramide and analgesic, drug or non-acidic analgesic in coordinated dosage forms, or the combination of metoclopramide and analgesic where the dosage form is an acid-base storage stabilized and coordinated dosage form. However, the prior art amply suggests the same as multi-delivery dosage forms, the combination of metaclopramide and analgesics, such as NSAIDs, are disclosed in the prior art. Further, the prior art discloses pretreating with metaclopramide when administering analgesics, such as NSAIDs, for treatment of migraine. As such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to modify the prior art as above with the expectation that analgesics, such as NSAIDs, as a class would be effective in treating migraine and that metoclopramide would increase the effectiveness and absorption of the analgesic. Further, one of ordinary skill in the art would have been motivated to formulate a dosage form wherein metoclopramide is immediate released and the analgesic coated by a sustained release coating, as it is known that pretreatment with metoclopramide overcomes the reduced gut motility associated with migraine, with the expectation that sustained release of the analgesic would increase effective treatment time and require less dosing, that the separation of the metoclopramide and analgesic by the coating of the analgesic would prevent any adverse interaction and that a single dosage form would be more convenient to administrate than separate

dosages of different drugs. Finally, although an acid-base storage stabilized form is not explicitly disclosed, the formulation of Shah et al. would result in the analgesic being coated and thus would not interact with the uncoated metoclopramide during storage. Further, one of ordinary skill in the art would be motivated to separate the analgesic from the metclopramide, at least one analgesic/metoclopramide combination has be found to be unstable.

Examiner has duly considered Applicant's arguments but deems them unpersuasive for the same reasons as above.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Conclusion

A facsimile center has been established in Technology Center 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier number for accessing the facsimile machine is 571-273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Choi whose telephone number is (571)272-0610. Examiner maintains a flexible schedule. However, Examiner may generally be reached Monday-Friday, 8:00 am – 5:30 pm (EST), except the first Friday of the each biweek which is Examiner's normally scheduled day off.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Mr. Gary Kunz, can be reached at 571-272-0887. Additionally, Technology Center 1600's Receptionist and Customer Service can be reached at (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

FIC
April 4, 2006

S. MARK CLARDY
PATENT EXAMINER
GROUP 1200 1617